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(54) Title: COMBINATION OF ORGANIC COMPOUNDS

(57) Abstract: The present invention relates to methods of treating sexual dysfunction associated with hypertension and another condition by administering a pharmaceutical combination of an angiotensin receptor blocker with either an anti-hypertensive drug or an HMG-CoA reductase inhibitor.

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Combination of Organic Compounds

Sexual dysfunction (SD) is more commonly observed in hypertensive patients especially those with diabetes and/or hyperlipidemia. Further, many commonly used anti-hypertensive drugs such as diuretics and beta-blockers can interfere with sexual function in both sexes, causing loss of libido, impairment of erectile function and ejaculation in men and delay or prevent orgasm in women. A specific angiotensin receptor blocker or antagonist (ARB), losartan, has been shown to have an advantage in preservation of sexual function when used clinically for the treatment of hypertensive disorder in male rats. Chan P. et al., *Pharmacology*, 58(3): 132-9 (1999). It has also been suggested that administration of ARBs result in smooth muscle relaxation and thus erection in an anesthetized dog. Kifor I. et al., *J. Urol.*, 157(5): 1920-1925 (1997). However, heretofore, there has not been a suitable treatment for SD associated with hypertension. Because of low response (40-55% efficacy) to antihypertensive monotherapy, combination therapy for hypertension (>80% efficacy) has to be used in a large number of patients.

Accordingly, there is a need for a method of treating a patient suffering from SD associated with hypertension comprising administering a therapeutically effective amount of a pharmaceutical combination to the patient, wherein the pharmaceutical combination comprise as active ingredients:

- (i) an ARB or a pharmaceutically acceptable salt thereof; and
- (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof. The pharmaceutical combination may be administered as a pharmaceutical composition comprising the pharmaceutical combination and a pharmaceutically acceptable carrier.

There is also a need for a method of treating a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia comprising administering a pharmaceutical combination to the patient, wherein the pharmaceutical combination comprise as active ingredients:

- (i) an ARB or a pharmaceutically acceptable salt thereof; and
- (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof.

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Toward these ends, and others, an aspect of the present invention provides a method of achieving a therapeutic effect for treating a patient suffering from SD associated with hypertension comprising administering a therapeutically effective amount of a pharmaceutical combination comprising as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof to a patient in need thereof.

In another embodiment of the present invention there is provided a method of achieving a therapeutic effect for treating a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia comprising administering a pharmaceutical combination to the patient, wherein the pharmaceutical combination comprise as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; and
(ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or
(b) a statin or a pharmaceutically acceptable salt thereof to a patient in need thereof.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of the present invention is greater than the sum of the effects that result from methods and compositions comprising the active ingredients of this invention separately.

The term "statin", where used in the specification and the appendant claims, is synonymous with the terms "3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitor" and "HMG-CoA reductase inhibitor." These three terms are used interchangeably throughout the specification and appendant claims. As the synonyms suggest, statins are

inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A reductase and, as such, are effective in lowering the level of blood plasma cholesterol. Statins and pharmaceutically acceptable salts thereof are particularly useful in lowering low-density lipoprotein cholesterol (LDL-C) levels in mammals, and particularly in humans.

In accordance with an aspect of the present invention there is provided a method of achieving a therapeutic effect for treating a patient suffering from SD associated with hypertension comprising administering a therapeutically effective amount of a pharmaceutical combination comprising as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof to the patient. In another embodiment of this aspect of the present invention the therapeutic effect achieved is synergistic, in that, the therapeutic effect is greater than the sum of the therapeutic effect achieved by the administration of the active ingredients separately.

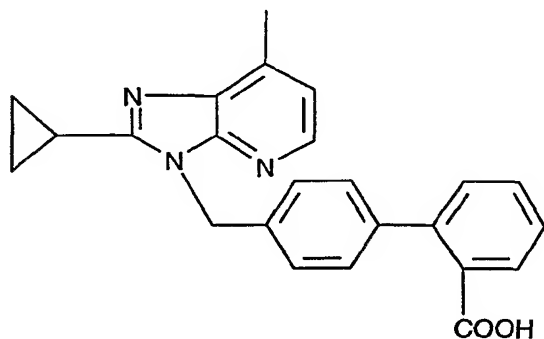
In another embodiment of the present invention there is provided a method of achieving a therapeutic effect for treating a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia comprising administering a pharmaceutical combination to the patient, wherein the pharmaceutical combination comprise as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof and (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof to the patient. In another embodiment of this aspect of the present invention the therapeutic effect achieved is synergistic, in that, the therapeutic effect is greater than the sum of the therapeutic effect achieved by the administration of the active ingredients separately.

In another embodiment of the present invention there is provided the use of a pharmaceutical combination comprising as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; and (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia.

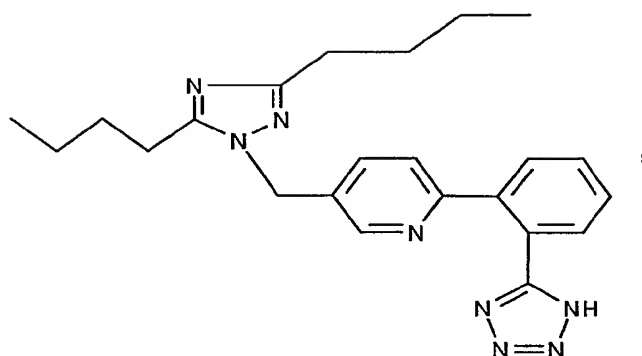
In another embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; and (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for the treatment of a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia.

ARBs (which are called AT₁-receptor antagonists and angiotensin II receptor antagonists) are understood to be those active ingredients which bind to the AT₁-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT₁ receptor, these antagonists can, for example, be employed as anti-hypertensives or for treating congestive heart failure.

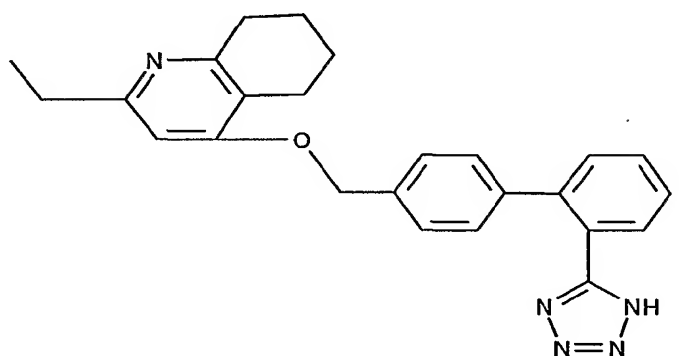
The class of ARBs comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of compounds selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula



the compound with the designation SC-52458 of the following formula



and the compound with the designation the compound ZD-8731 of the following formula



or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ARBs are those agents which have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

Anti-hypertensive drugs within the scope of the present invention include, but are not limited to, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, diuretics, vasodilators, ARBs, α and β adrenergic blockers and renin inhibitors as well as combinations of the above, for example, ACE inhibitors plus one of CCBs and diuretics and α and β adrenergic blockers plus diuretics.

Examples of CCBs useful in the combinations of the present invention are selected from the group consisting of diltiazem, nifedipine, nitrendipine, nimodipine, niludipine, niguldipine, nicardipine, nisoldipine, amlodipine, felodipine, isradipine, ryosidine, verapamil, gallopamil and tiapamil or in each case a pharmaceutically acceptable salt thereof.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents which have been marketed, most preferred are benazepril and enalapril or pharmaceutically acceptable salt thereof.

The class of diuretics include carbonic anhydrase inhibitors such as diclorphenamide; loop diuretics such as bumetanide, torsemide, ethacrynic acid and furosemide; potassium-sparing diuretics such as spironolactone, triamterene and amiloride; and thiazides such as hydroflumethiazide, chlorothiazide, hydrochlorothiazide, methychlothiazide, metolazone and chlorthalidone or, in each case, a pharmaceutically acceptable salt thereof.

Vasodilators include nitroglycerin and isosorbide mono- and di- nitrate.

β adrenergic blockers include propranolol, bisoprolol and metoprolol.

Renin inhibitors inhibit the action of the natural enzyme renin. The latter passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. That increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of e.g. the hypotensive effect of renin inhibitors.

Renin inhibitors include especially non-peptidic representatives, preferably aliskiren (2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide, being specifically disclosed

in EP 678503 A); especially preferred is the hemi-fumarate salt thereof; detikiren (cf. EP 173481A); terlakiren (cf. EP 266950 A); and zankiren (cf. EP 229667 A). Especially preferred is aliskiren, preferably the hemi-fumarate thereof.

Statins include atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, and simvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred statins are those agents which have been marketed, most preferred are fluvastatin, simvastatin, atorvastatin, or pitavastatin or a pharmaceutically acceptable salt thereof.

Preferred combinations according to the present invention comprise the combination of valsartan and an anti-hypertensive drug selected from the group consisting of the CCB amlodipine, especially the besylate thereof, the ACEI benazepril, the ACEI enalapril, the diuretic hydrochlorothiazide, the β -adrenergic blocker metoprolol, the statin fluvastatin, the statin pitavastatin, and the renin inhibitor aliskiren, or, in each case a pharmaceutically acceptable salt thereof.

The combination according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable nontoxic acids or bases including inorganic acids and bases. Suitable pharmaceutically acceptable acid salts for the first agent and the co-agents of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like.

The pharmaceutical compositions of the present invention comprise the pharmaceutical combinations as described above plus a pharmaceutically acceptable carrier.

“SD associated with hypertension” as that term is used herein means the incidence of sexual dysfunction resulting from hypertension as well as from the medical treatment of hypertension with drugs irrespective of the presence of diabetes and hyperlipidemia.

“SD associated with hypertension and another condition, including but not limited to hyperlipidemia and diabetes” as that term is used herein means the incidence of sexual dysfunction resulting from these conditions.

The treatment of SD associated with hypertension and the treatment of SD associated with hypertension and another condition by methods described in the present invention may be demonstrated in the following pharmacological test:

An international, multi-center, double-blind, randomized, active-controlled trial, is conducted in approximately 14000 patients with essential hypertension and moderate to high cardiovascular risk profiles. In this trial, valsartan or amlodipine are administered as monotherapy. Dosages, e.g. once a day, are as follows: Valsartan is administered in 40, 80, or 160 mgs; amlodipine is administered in 2.5, 5 or 10 mgs.

For combination therapy, valsartan is administered in combination with one of amlodipine, simvastatin or hydrochlorothiazide (HCTZ). During the development of these combinations, valsartan is administered once or twice daily at 40, 80, 160 or 320 mgs. Co-administered with valsartan is Amlodipine at a dose of 2.5, 5 or 10 mgs; simvastatin at a dose of 20, 40 or 80 mgs or HCTZ at a dose of 12.5 or 25 mgs.

After the administration of the above monotherapies and combinations patients are evaluated for quality of life, including sexual function. Applicant has surprisingly found that the combinations described above achieve a therapeutic effect of lowering sexual dysfunction in the patients greater than the therapeutic effect achieved by the sum of the administration of the active ingredients separately.

Further, administration of pharmaceutical combinations of the invention have a therapeutic effect for (i) reducing sexual dysfunction associated with hypertension and (ii) reducing sexual dysfunction associated with hypertension and another condition. The administration of these combinations also achieves a synergistic therapeutic effect for (i)

reducing sexual dysfunction associated with hypertension and (ii) reducing sexual dysfunction associated with hypertension and another condition which effect is greater than the sum of the therapeutic effect achieved by administration of the active ingredients separately.

To prepare the pharmaceutical compositions of the present invention, the active ingredients, or their pharmaceutically acceptable salts, racemates or enantiomers are combined in intimate admixture by mixing, blending or combining in any manner known to those of skill in the art, with a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may take a wide variety of forms depending on the form of preparation desired for administration. As an example, the pharmaceutical compositions comprise of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 % of the active ingredients.

Any suitable route of administration may be employed for providing a mammal with a therapeutically effective amount of the pharmaceutical combinations and compositions of the present invention. For example, oral, rectal, vaginal, topical, parental (subcutaneous, intramuscular, intravenous, transdermal) and like forms of administration may be employed. Dosage formulations include ointments, foams, gels, transdermal patches, tablets (both fractionable and non-fractionable), caplets, powders for inhalations, gelcaps, capsules, elixirs, syrups, chewable tablets, lozenges, troches, dispersions, aerosols, solutions, fast-dissolving wafers, suppositories or suspensions or other known and effective delivery methods.

Oral dosing is preferred. In preparing the compositions in oral dose form, any of the usual pharmaceutical carriers may be employed including any material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying, formulating or transporting a chemical agent. Specific examples are water, glycols, oils, alcohols and the like in the case of oral liquid preparations. In oral solid forms solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be employed. Oral

solid preparations are preferred over the oral liquid preparations. A preferred oral solid preparation is capsules and tablets, because of their ease of administration.

For parental compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises PEG, saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect on the skin. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient(s) calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and the combination can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

The total daily dose range may be administered in a range of from about 0.01 mg to about 1000 mg. The daily dose range may be about 800 mg, 600 mg, 400 mg, 200 mg, 100 mg, 50 mg, 20 mg, 10 mg, 5 mg, 1 mg, .1 mg or .01 mg. Preferably, a daily dose range should be between about 2.5 mg to about 540 mg, while most preferably, a daily dose range should be between about 5 mg to about 100 mg. It is preferred that the doses are administered OD (once daily) or BID (2 times a day). In managing the patient, the therapy should be initiated at a lower dose, perhaps about 5 mg to about 10 mg, and increased up to about 50 mg or higher depending on the patient's response. It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The term "therapeutically effective amount" is encompassed by the above-described molar ratio and dosage amounts and dose frequency schedule.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Valsartan, as a representative of the class of AT₁-receptor antagonists, is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 mg to about 320 mg, of valsartan which may be administered to patients, preferably from about 80 mg to about 320 mg. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

In case of calcium channel blockers, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 2.5 mg to about 540 mg, preferably, when using amlodipine, for example, about 2.5 mg to about 10 mg administered once a day; about

180 mg to about 540 mg of verapamil once a day; about 120 mg to about 360 mg of diltiazem and about 2.5 mg to about 20 mg of isradipine once a day.

In case of ACE inhibitors, preferred dosage unit forms of ACE inhibitors are, for example, tablets or capsules comprising e.g. from about 10 mg to about 80 mg, preferably 10 mg, 20 mg or 40 mg, of benazepril and from about 2.5 mg to about 20 mg, preferably 2.5 mg, 5 mg, 10 mg or 20 mg, of enalapril.

In case of Beta blockers, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 80 mg to about 640 mg of propranolol; from about 2.5 mg to about 20 mg of bisoprolol and from about 50 mg to about 400 mg, of metoprolol.

In case of statins, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 20 mg to about 80 mg of fluvastatin; from about 10 mg to about 80 mg of atorvastatin and from about 5 mg to about 80 mg of simvastatin, administered once a day.

Especially preferred are low dose combinations.

EXAMPLES

The present invention is further described by the following examples. The examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplifications, while illustrating certain specific aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

Formulation Example 1:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur

Colloidal anhydrous silica / Colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / Colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water ^{*)}	-	
DIOLACK pale red 00F34899	7.00	
Total tablet mass	167.00	

^{*)} Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tableting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan.

Formulation Example 2:

Film-coated tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur

Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry Light Brown 00F33172	10.00	
Total tablet mass	330.00	

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 3:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Core: Internal phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
External phase		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF

Magnesium stearate [Lubricant]	2.00	USP/NF
Film coating		
Opadry® brown OOF 16711 ^{*)}	9.40	
Purified Water ^{**)}	-	
Total tablet mass	199.44	

^{*)} The composition of the Opadry® brown OOF16711 coloring agent is tabulated below.

^{**)} Removed during processing

Opadry® Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172)	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50
Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 4:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	

Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

Granulation/Drying

Valsartan and microcrystalline cellulose are spray-granulated in a fluidized bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidized bed dryer.

Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical screw type mixer for approximately 10 minutes.

Encapsulation

The empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filled capsules are dedusted, visually inspected, weight checked and quarantined until by Quality assurance department.

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00

Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	342.00

The formulation is manufactured e.g. as described in Formulation Example 4.

Formulation Example 6:

Hard Gelatin Capsule:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

Examples 7 to 11:

Example	7	8	9	10	11
Components	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)
Granulation					
Valsartan Drug Substance	80.000	160.00 0	40.000	320.00 0	320.00 0
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	54.000	108.00 0	27.000	216.00 0	216.00 0
Crospovidone (NF, Ph.Eur.)	15.000	30.000	7.500	80.000	60.000
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.000	0.750	3.000	6.000
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	1.500	10.000	12.000
Blending					
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	---	---	---	3.000	-
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	0.750	8.000	6.000
Core Weight/mg	155.000	310.00 0	77.500	640.00 0	620.00 0
Coating	-	-	3.800	15.000	16.000

Example 12:

Hard gelatin capsule:

Component	Amount per unit [mg]
Capsule	
Fluvastatin Sodium ¹⁾	21.481 ²⁾
Calcium Carbonate	62.840
Sodium Bicarbonate	2.000
Microcrystalline Cellulose	57.220
Pregelatinized Starch	41.900
Purified Water ³⁾	Q.S.
Magnesium Stearate	1.050
Talc	9.430
Target Capsule Fill Weight	195.92
Capsule Shell	
Hard gelatin Capsule Shell	48.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	244.42

¹⁾ includes a 2% overage for moisture²⁾ 20 mg of free acid is equivalent to 21.06 mg Na salt³⁾ partially removed during processing

Example 13:

Hard gelatin capsule

Component	Amount per unit [mg]
Fluvastatin Sodium	42.962 ^{1) 2)}
Calcium Carbonate	125.680
Sodium Bicarbonate	4.000
Microcrystalline Cellulose	114.440
Pregelatinized Starch	83.800
Purified Water ³⁾	Q.S.
Magnesium Stearate	2.100
Talc	18.860
Target Capsule Fill Weight	391.840
Capsule Shell	
Hard gelatin Capsule Shell	76.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	468.34

¹⁾ includes a 2% overage for moisture²⁾ 20 mg of free acid equivalent to 21.06 mg Na salt³⁾ partially removed during processing

Example 14:

Round, slightly bi-convex, film-coated tablets with beveled edges:

Component	Amount per unit [mg]
Table Core	
Fluvastatin Sodium ¹⁾	84.24 ²⁾
Cellulose Microcrystalline / Micro-crystalline cellulose fine powder	111.27
Hypromellose / Hydroxypropyl methyl cellulose (Methocel K100LVP CR; HPMC100 cps)	97.50
Hydroxypropyl cellulose (Klucel HXF)	16.25
Potassium hydrogen carbonate / Potassium bicarbonate	8.42
Povidone	4.88
Magnesium stearate	2.44
Core Tablet Weight	325.00
Coating	
Coating premix - Opadry Yellow (00F22737)	9.75
Total Weight	334.75
Water, purified ³⁾	Q.S.

¹⁾ 84.24 mg of the sodium salt of fluvastatin is equivalent to 80 mg of fluvastatin free acid

²⁾ to be adjusted for moisture (LOD)

³⁾ removed during processing

Example 15 :

Round, biconvex, beveled-edged, film-coated tablets

Component	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]
Benazepril Hydrochloride	5.00	10.00	20.00	40.00
Lactose Monohydrate, NF	142.00	132.00	117.00	97.00
Pregelatinized Starch, NF	8.00	8.00	8.00	8.00
Colloidal Silicon Dioxide, NF (Cab-O-Sil, M-5)	1.00	1.00	1.00	1.00
Crospovidone, NF	3.00	3.00	3.00	3.00
Microcrystalline Cellulose, NF	18.00	18.00	18.00	24.25
Hydrogenated Castor Oil, NF	8.00	8.00		
Magnesium Stearate, NF			8.00	1.75
Color:	-			0.50
Yellow-Brown (suspension)		2.00		
Red-Brown (suspension)			0.50	
Purified Water, USP	Trace	trace	trace	trace
Opadry Color:				
Yellow	8.38	8.38		
Pink			8.38	8.38
Total	193.38	190.38	183.88	183.88

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible without departing from the spirit and scope of the preferred versions contained herein. All references and Patents (U.S. and others) referred to herein are hereby incorporated by reference in their entirety as if set forth herein in full.

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical combination comprising as active ingredients (i) an ARB or a pharmaceutically acceptable salt thereof; and (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a patient suffering from SD associated with hypertension and another condition.
2. The use according to claim 1 or 2 wherein another condition that is associated with SD is diabetes or hyperlipidemia.
3. The use of any one of claims 1 – 3 wherein the ARB, anti-hypertensive drug or HG-CoA reductase inhibitor, respectively, include pharmaceutically acceptable racemates or enantiomers thereof.
4. The use of any one of claims 1 – 3 wherein the ARB is selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, E-1477, SC-52458 and ZD-8731.
5. The use of claim 4 wherein the ARB is valsartan.
6. The use of any one of claims 1 - 3 wherein the anti-hypertensive drug is selected from the group consisting of one or more of CCBs, ACE inhibitors, diuretics, vasodilators, ARBs, α and β adrenergic blockers, ACE inhibitors in combination with CCBs, diuretics, α and β adrenergic blockers, and diuretics.
7. The use according to any one of claims 1 – 3 wherein the anti-hypertensive drug is a renin inhibitor or a pharmaceutically acceptable salt thereof.
8. The method according to any one of claims 1 – 3 and 6 wherein the CCBs are selected from the group consisting of diltiazem, nifedipine, nitrendipine, nimodipine, niludipine, niguldipine, nicaldipine, nisoldipine, amlodipine, felodipine, isradipine, ryosidine, verapamil, gallopamil and tiapamil.

9. The use according to any one of claims 1 to 3 and 6 wherein the ACE inhibitors are selected from the group consisting of alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, andtrandolapril.

10. The use according to any one of claims 1 – 3 and 6 wherein the diuretics are selected from the group consisting of carbonic anhydrase inhibitors, combination diuretics, loop diuretics, potassium-sparing diuretics and thiazides.

11. The use according to claim 10 wherein the thiazides is hydrochlorothiazide.

12. The use according to any one of claims 1 – 3 and 6 wherein the vasodilators are selected from the group consisting of nitroglycerin and isosorbide mono- and di- nitrate.

13. The use according to any one of claims 1 – 3 and 6 wherein the β adrenergic blockers are selected from the group consisting of propranolol, bisoprolol and metoprolol.

14. The use according to any one of claims 1 – 3 and 6 wherein the renin inhibitors are selected from the group consisting of aliskiren; detikiren; terlakiren; and zankiren or a pharmaceutically acceptable salt thereof.

15. The use according to any one of claims 1 – 3 wherein the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, and simvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

16. The use according to any one of claims 1 - 3 wherein the combination comprises valsartan and an anti-hypertensive drug selected from the group consisting of amlodipine, especially the besylate thereof, benazepril, enalapril, hydrochlorothiazide, metoprolol, fluvastatin, pitavastatin, and aliskiren, or, in each case a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition for the treatment of a patient suffering from SD associated with hypertension and another condition, comprising as active ingredients (i)

an ARB or a pharmaceutically acceptable salt thereof; and (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or (b) a statin or a pharmaceutically acceptable salt thereof.

18. A method of treating a patient suffering from SD associated with hypertension and another condition, including but not limited to diabetes and hyperlipidemia comprising administering a pharmaceutical combination to the patient, wherein the pharmaceutical combination comprise as active ingredients:

- (i) an ARB or a pharmaceutically acceptable salt thereof; and
- (ii) (a) an anti-hypertensive drug or a pharmaceutically acceptable salt thereof or
(b) a statin or a pharmaceutically acceptable salt thereof.